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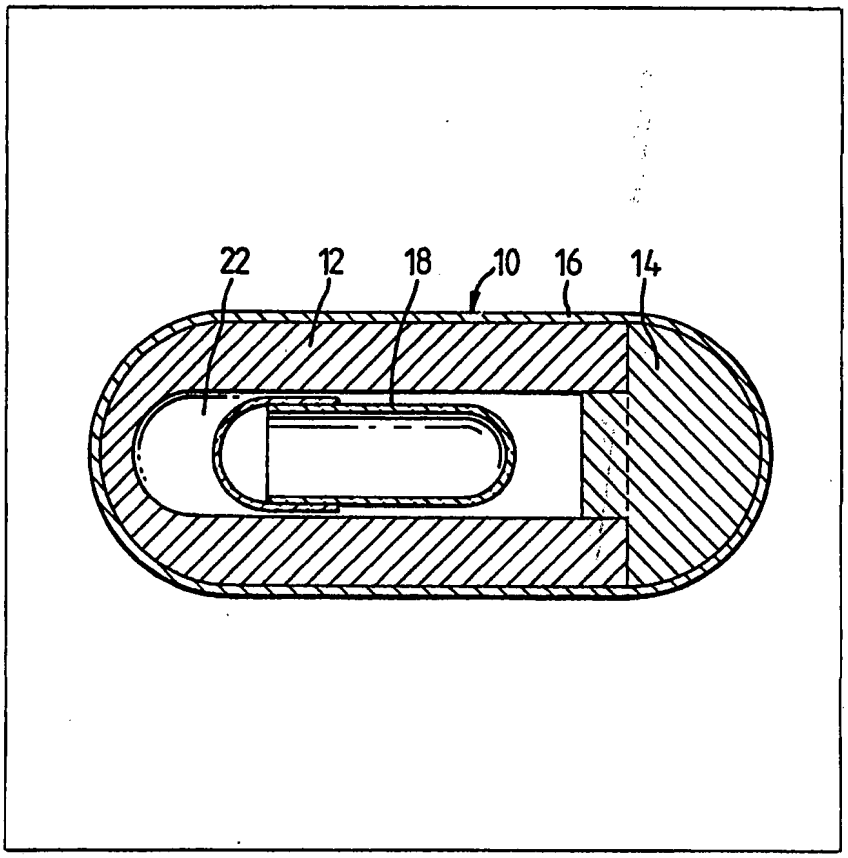
(54) Compound capsule

(57) A capsule assembly for oral administration of a prophylactic drug includes a frangible outer capsule 10 and an inner edible capsule 18 which is soluble in digestive juices. An air-space 22 is provided between the two capsules to permit the user to bite through the outer capsule and swallow the inner capsule intact. The drug may be an antidote to nerve gas.



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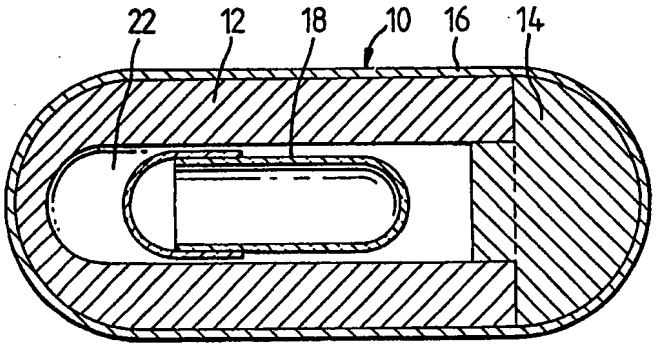

SPECIFICATION

Compound capsule

This invention relates to containers for the oral administration of prophylactic drugs for internal medical application.

It is highly desirable that certain drugs be taken by mouth by military personnel immediately before or after they have been subjected to attack by persistent liquid nerve gas. The drugs, if taken in time, act in a prophylactic way to prevent or ameliorate poisoning by nerve agent penetrating the clothing and skin However, under the anticipated circumstances of chemical attack, the immediate defensive actions of highest priority are a) to put on a protective mask, b) to close all openings in protective clothing, and c) to carry out personal decontamination procedures. These actions make it extremely difficult or impossible to take drugs by mouth, because of the danger of contaminating the capsules while preparing to take them in a contaminated environment, while dressed in a contaminated suit and mask, and wearing heavy contaminated protective gloves.

The alternative of having all personnel take drugs on a (4 times daily) routine basis in anticipation of attack is open to serious objections, because it is likely adversely to affect the health and efficiency of the recipients, and it would be an additional unnecessary disciplinary burden to enforce compliance, unlikely to succeed completely, particularly in the absence of an immediate credible threat of chemical attack.

At present, in order to take prophylactic drugs by mouth, the seal of the mask to the face must be opened, and special precautions taken to get the dosage into the mouth without introducing contamination.

It is not certain that the present arrangement is entirely safe, and it requires considerable training.

Various alternative solutions have been proposed including providing a water-proof coated single capsule held in the mouth and swallowed at the time of detection of chemical attack. The disadvantage of this is that the waterproof coating would delay or prevent absorption of the drug. If this type of capsule is bitten open at the time of detection of chemical attack, the drug which is typically in loose powder form would be released into the mouth. Difficulty in swallowing without water is the obvious disadvantage. A capsule of this type is described in Canadian Patent No. 315,720, which issued 29 September 1931 to G H Lee et al.

According to the present invention a novel capsule assembly is provided, for oral administration of a prophylactic drug, said assembly comprising an outer capsule of an edible frangible material presenting an outer surface of an edible material which is insoluble in digestive juices; an inner capsule of an edible material which is soluble in digestive juices, disposed within said outer capsule and containing said prophylactic drug; and an airspace between said inner and outer capsules, the arrangement being such that said outer capsule can be broken leaving the inner capsule free to be swallowed intact.

The proposal is to provide a prophylactic drug mixture which would be held in reserve within the cheek pouch continuously while the chemical protective ensemble is worn in the open state (ie garment zipper open, mask in haversack, hood open, steel helmet worn).

In response to a liquid spray attack with an unidentified chemical agent, the ensemble would be closed immediately (ie., mask donned, zipper closed, steel helmet replaced) according to the prescribed masking drill.

The action of biting open the outer capsule and swallowing the inner capsule containing the drug mixture would be taken if, and only if the spray attack were identified as a nerve agent, whether by use of local detector papers, by central command based on more sophisticated detection systems, or by medical diagnosis of casualties. The biting action would take place with the protective ensemble remaining closed (mask on).

In the event of no identified nerve gas attack, the drug capsule would remain in the cheek, to be discarded and replaced by a fresh capsule at the time of unmasking or later. The presence of the capsule in the cheek need not prevent eating or drinking when unmasked.

In the drawing which serves to illustrate the preferred embodiment of the invention, the figure is a side elevation in section of the novel capsule assembly.

Referring specifically to the drawing, it is seen that the assembly comprises an outer capsule 10 of a suitable frangible edible material, including a tubular body portion 12 and an end closure cap 14. The outer capsule 10 is sealed together by a substantially uniform coating 16 of a suitable edible material which is insoluble in digestive juices, on the exterior thereof. An inner capsule 18 of a suitable edible material which is soluble in digestive juices is provided within outer capsule 10. The inner capsule 18 contains an appropriate dosage of a prophylactic drug, typically in powder form. An air space 22 is provided between inner and outer capsules and is arranged such that when the outer capsule is broken by biting, the inner capsule is free to be swallowed intact.

Thus, the double capsule provides the drug dosage at the required time relative to the spray attack, and in a form which allows prompt and reliable absorption of the drug from the gastrointestinal tract into the blood stream.

It is important that absorption be prompt and reliable, so that the drug will arrive in the blood stream coincident with the onset of symptoms of nerve gas poisoning. For liquid nerve gas on bare skin, symptoms occur approximately 30 to 60 minutes after contact with a lethal dose.

The inner capsule, preferably made of gelatin, has two additional advantages: (a) it can be swallowed without a drink of water, which would not be immediately available to a man in a mask, and (b) standard 2-piece gelatin capsules are readily available commercially and can be filled without access to manufacturing machinery. This enables double capsules to be made by hand quickly and cheaply.

The air space between the outer waterproof capsule and the inner gelatin capsule has two important functions: (a) it allows the gelatin capsule to emerge free of any coating, and undamaged, when the outer capsule is bitten open. The inner gelatin capsule is then ready to swallow without water and (b) it allows sufficient clearance so that standard commercial gelatin capsules can be loaded into the preformed outer capsule bodies by a simple hand operation.

It is intended that the outer capsule can be bitten open, and the fragments chewed and swallowed after the inner gelatin capsule. The outer capsule must protect the inner gelatin capsule from the moisture and mechanical action of the mouth for a holding period at least equal to the maximum time expected for troops to remain masked. Ideally, the outer capsule should withstand a 12 hour holding period, and 6 hours would be the minimum normally acceptable. The capsules would be discarded and replaced after that time.

The outer capsule is designed intentionally to be sufficiently large, to prevent accidental swallowing without biting open.

The material of the body and cap of the outer capsule must be sufficiently frangible to break up on biting, to allow the inner gelatin capsule to be free to be swallowed intact. The fragments must then be chewable into small bits for swallowing, after the inner gelatin capsule has been swallowed.

The coating on the exterior surface of the outer capsule has the essential function of protecting the body of the outer capsule from the digestive juices in the mouth during the holding period. If this coating were not present, or if it leaks, the body of the outer capsule would disintegrate before the end of the holding period.

An additional function of the coating is to cement the cap to the body of the outer capsule. The coating material is preferably of an edible wax such as paraffin wax of beeswax. Carnauba wax is also contemplated.

Such a coating has the advantage that it is recognised as being harmless when taken by mouth.

A test program has been carried out with civilian volunteer human subjects to determine:

(1) whether the prototype capsule assembly could be held in the mouth for 6 hours without interfering with normal eating and drinking;

(2) whether the prototype capsule assembly deteriorated or disintegrated during the holding period; and

(3) whether the prototype capsule assembly could be opened by chewing the inner capsule swallowed, and the residue chewed and swallowed by the volunteer subjects while wearing a protective mask.

METHODS

Volunteers who were in possession of a Canadian Forces protective mask, were recruited from the DRES General Volunteers list without further medical screening. All subjects were well acquainted with the circumstances of and response to chemical attack, and the use of the mask.

Each volunteer was given a capsule assembly, with the inner gelatin capsule empty; he was directed to hold the capsule in his mouth in his cheek continuously, for 6 hours if possible commencing at approximately 0900 hrs. The volunteer was also asked to report to the trial director the time of occurrence of any softening or disintegration of the outer capsule. The volunteers retained the capsule assemblies in the mouth while taking their customary mid-morning coffee and lunch.

At the end of the six-hour period, the assembly was examined for signs of deterioration, or was replaced if it had failed during the holding period. The volunteer then put on his protective mask and proceeded to bite open the outer capsule, to swallow the gelatin capsule, and to chew and swallow the remnants of the outer capsule.

RESULTS

The first three tests were carried out with prototype capsule assemblies which had been given a single thin coat of of wax ie about 0.02 inches, and had been stored at room temperature for approximately nine months. All three softened and failed approximately 30 minutes after the

start of the holding period.

Ten tests were carried out with capsule assemblies which has been freshly coated with a double layer of wax ie about 0.03 inches. The results are shown in Table 1 of the ten subjects, seven completed the 6-hour holding period with capsule assemblies intact; the outer coating failed in two cases and the capsule was unintentionally bitten in one case.

Table 1
Summary of Capsule Holding Tests

	Volunteer Subject No.	Capsule Holding Time-hours	Capsule Condition
Capsules with thin (about 0.02 inches) wax coatings	1	0.5	soft
	2	0.6	soft
	3	0.5	soft
	4	6	intact
	5	6	intact
	6	5	soft
Capsules with thick (about 0.03 inches) wax coatings	7	6	intact
	8	6	intact
	9	6	intact
	10	6	intact
	11	3	bitten & soft*
	12	6	intact
	13	3.5	soft

*subject accidentally bit capsule while eating.

Minor annoyance and light discomfort was experienced in holding the assembly in the cheek for long periods, which was attributed to the size of the diameter of the assembly, rather than the length.

All thirteen subject were able to open an intact assembly by biting, while wearing a Canadian Armed Forces protective mask and to swallow the gelatin capsule and the remnants of the outer capsule

The results show that capsules containing prophylactic drugs can be held in reserve in the mouth for six hours or longer, with no more than slight discomfort, and without preventing normal eating and drinking. It is concluded that the concept of initiating drug prophylaxis after completion of the masking drill and confirmation of the presence of nerve gas, and without removing mask or gloves, is technically feasible. It is also apparent that the useful lower limit of the thickness of the wax coating is about 0.03 inches. The wax coating cannot be too thick as to prevent biting ease. An operable thickness range of 0.03–0.06 inches is therefore contemplated.

The edible frangible material used for the outer capsule is preferably a mixture of whole wheat flour and molasses, baked hard, and coated with paraffin wax. It is also contemplated to employ a white or colourless material instead of whole wheat flour, in order that the assemblies could be colour coded with food colouring, to identify the different dosage forms which may be required. Since the fibre content of whole wheat flour appears important in giving mechanical strength and good moulding qualities (a) bleached whole-wheat flour, (b) white flour with addition of pure cellulose powder could be used. Corn syrup could be used instead of molasses.

Preparation of Edible Material

Molasses — 2 parts by volume
Whole wheat flour — 4 parts by volume

Heat molasses to boiling. Add flour portionwise, with thorough mixing to produce a homogeneous plastic mass. Form into a ball, and wrap in waxed paper and foil for preservation.

Fabrication of Edible Capsules and Caps

Approximately 2 g. of the edible material is formed into a ball; this is then formed with the fingers over a cylindrical brass mandrel of diameter slightly greater than the outside diameter of the gelatin capsule to be used; the material is moulded to form a hollow cylinder with one end closed. The mandrel with material moulded on it is placed in a brass holder.

The caps are made by forming approximately 3.0 g of the edible composition into a drill-hole of suitable diameter and depth in a brass block.

After moulding, the capsules and caps are heated to 350°F. for 10 minutes, and allowed to cool to room temperature, before freeing from the brass forms. The edible pieces are then trimmed to final size by means of a jeweller's saw.

Assembly and Waxing

The outer surface of the capsules and caps are coated with melted paraffin or beeswax. The gelatin capsule containing the powdered drug in unit dosage form is placed loosely inside the edible outer capsule, and the cap is sealed on with melted wax. The seam between cap and capsule is now smoothed by sandpapering away any rough edges, and a final coat of hot wax is applied with a brush. The outer capsule could be pre-coated with wax before final assembly.

The following prophylactic drugs adapted for oral administration are comtemplated.

(1) A reversible cholinesterase inhibitor, for example Pyridostigmine Bromide, dose 30 to 60 mg.

(2) A peripherally acting parasympatholytic drug, for example propantheline Bromide, dose 15 to 30 mg.

(3) A benzodiazepine tranquillizer, with anticonvulsant properties against nerve gas convulsions, for example, Diazepam, dose 5 to 10 mg.

(Note. The dosage has been shown as a range, because dose may be varied with body weight. All drugs to be powders)

(4) A combination of two or three of the drugs mentioned above.

CLAIMS

1. A capsule assembly, for oral administration of a prophylactic drug, comprising

an outer capsule of an edible frangible material presenting an outer surface of an edible material which is insoluble in digestive juices;

an inner capsule of an edible material which is soluble in digestive juices, disposed within said outer capsule and containing said prophylactic drug; and

an airspace between said inner and outer capsule, the arrangement being such that said outer capsule can be broken leaving the inner capsule free to be swallowed intact.

2. A capsule assembly according to claim 1, wherein said coating is of wax selected from the group consisting of beeswax, paraffin wax, and carnauba wax.

3. A capsule assembly according to claim 1 or claim 2, wherein the thickness of said coating is 0.03 to 0.06 inches.

4. A capsule assembly according to any one preceding claim, wherein said inner capsule is made of gelatin.

5. A capsule assembly according to claim 4, wherein the thickness of the wax coating is about 0.03 inches.

6. A capsule assembly according to claim 4, wherein said outer capsule is made of a mixture of 4 parts by volume of whole wheat flour and 2 parts by volume of molasses, baked hard.

7. A capsule assembly according to any one preceding wherein the prophylactic drug is in powder form.

8. A capsule assembly according to any one preceding claim, wherein said prophylactic drug is selected from the group consisting of a reversible cholinesterase inhibitor, a peripherally acting parasympatholytic drug, a benzodiazepine tranquillizer, with anti convulsant properties and mixtures thereof.

9. A capsule assembly according to claim 1 and substantially as hereinbefore described.

10. A capsule assembly substantially as hereinbefore described with reference to the accompanying drawing.

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